## REMARKS

Applicants request further examination, and reconsideration and withdrawal of all outstanding rejections for at least the reasons stated below. These remarks are believed to be fully responsive to all outstanding rejections, and put the application in condition for allowance.

### Novelty

It is asserted that claims 11-12 are anticipated by Bhutani. Applicants traverse the rejection.

*Bhutani*

Bhutani describes a controlled release pharmaceutical formulation wherein an active ingredient is coated on non-pareil beads, or onto drug crystals or granules (col 4, lines 11 to 13). The resulting pellets are then coated with varying amounts of a retarding material, and then coated with several layers of disintegrating agent or agents (col 4, lines 20 to 24). Bhutani distinguishes his invention over prior art medicaments by highlighting the fact that the art fails to describe a "uniform coating of a retarding material on a medicament-containing particle overlaid with a uniform coating of disintegrant material and then compressed into a dense tablet that breaks up quickly in the body." (col. 3, lines 44-48).

As stated in the specification, such added ingredients and layers complicate the formulation and add to the unpredictability in the qualities of the resulting tablets. They also confer to the granules compressibility and tableting behavior entirely different from the claimed neutral granules coated with a single layer of uncoated active principle. Specification, p. 10, lines 4-30. The instant claims expressly require

that 99-100% of the formulation is neutral microgranules coated with active principle (and optional binder), the remainder being lubricant. Thus, the claimed tableting premix does not tolerate the added coatings of Bhutani, and the claimed invention is novel over Bhutani.

*Harrison*

Applicants traverse the rejection of claims 11-12 as anticipated by Harrison. Harrison describes beads having an inert particulate core, and adhered thereto is a coating comprising the active agent. Each of Harrison's beads is coated with a sustaining coating comprising at least three polymers (col 3, lines 48 to 68; col. 5, lines 12 to 14). The various polymers must be carefully selected to be soluble at various and distinct pH ranges (col. 3, lines 48-68). The selection and proportionate composition of those polymers in creating the coating is represented as important in achieving the uniform release of the medicament (e.g., col. 4, lines 53-56). Thus, Harrison teaches that those polymers, which do not constitute elements of the instant claims, are essential components of the Harrison formulation.

As argued above with respect to Bhutani, the presently claimed formulation does not accommodate the added layers, coatings, and polymers required of various formulations in the prior art, and particularly those of the Harrison reference. Thus, the invention of claims 11-12 is novel over Harrison.

*Hsiao*

Applicants traverse the rejection of claims 11-12 as anticipated by Hsiao. As acknowledged in the rejection, Hsiao discloses nonpareil seeds coated with quinidine, which are then coated with a mixture of about one and one-half to about nine parts by weight hydroxypropylcellulose (col. 1 lines 12 to 21); and each pellet

is coated to about 5-15% of its weight with that coating mixture. Further, Hsiao teaches that a carefully balanced quantity of the coating mixture is essential to achieve the requisite release characteristics of the dosage form (col. 1, lines 49-64).

As argued above, the claimed formulation does not accommodate the added layers and coatings required of the Hsiao formulations; nor does the claimed formulation rely on such coatings to control the release characteristics of the active principle. Quite the opposite, the instant formulations dispense with such coatings altogether. Thus, the tableting premix as claimed in claim 11-12, is novel over Hsiao.

**Non-obviousness**

*Barry & Makino*

It is also asserted that pending claims would have been obvious to one of ordinary skill in the art over Barry in view of Makino. Applicants traverse the rejection.

Barry discloses a tablet composed of two parts: a matrix or a binder; and a quantity of small pellets distributed therein (col. 1, lines 27 to 36). Although Barry describes the use of nonpareil seeds as the pellets, the pellets are dispersed within a substantial quantity of a binder or matrix. As such, the Barry formulation differs from a formulation consisting essentially of neutral microgranules individually coated with an active agent mixture, as recited in the instant claims.

In Barry, the binder or matrix is about 30-70% of the weight of the formulation. See, e.g., Fig. 1 and cols 2-3. The matrix material contributes substantially to the desired friability of the tablet (e.g., friable under thumb

pressure). Col. 2, lines 18-59. The substantial quantity of matrix or binder required by Barry is not accommodated by the instant claims, which require that the tablet *consist essentially of* neutral microgranules coated with an active principle mixture and less than 1% of a compression excipient. The binder or matrix material of Barry is expressly excluded by the instant formulation. Barry does not teach or suggest a tablet consisting essentially of neutral microgranules each individually coated with an active principle mixture and less than 1% compression excipient.

Further, Barry teaches that the pellets embedded in a substantial quantity of matrix material must be sealed by a protecting or barrier coating, whose thickness or characteristics are chosen to effect disintegration within various portions of the alimentary canal (e.g., col. 3, lines 15-70). The presently claimed formulations do not contain such components. Barry thus does not teach or suggest the claimed tablets that are devoid of such coatings.

Makino does not remedy the deficiencies of Barry. Makino is directed to the preparation of granules for use as they are or in capsules (col. 1, lines 8-14). The spherical granules may be coated with a sustained-release coating, a gastric coating, an enteric coating or a taste-masking coating (col. 4, lines 15-19 and 30-34).

Makino does not teach that the spherical granules are directly compressible, nor that they might be suitable for being compressed into tablets. Thus, one skilled in the art would have found within the reference no basis or suggestion to incorporate the teachings of Makino into an effort to produce a compressible tablet as claimed. And, even if one had found such a suggestion, there is nothing within either reference that would have afforded a well reasoned

basis for expecting success in doing so. That is, neither Barry nor Makino, nor the combination would have led one skilled in the art to expect that one could reliably formulate a mixture of neutral microgranules coated with only an active agent mixture in combination with only 1% compression excipient into tablets. Indeed, Barry teaches the opposite, requiring substantial quantities of matrix material; and Makino affords no teaching whatsoever that one could dispense with that matrix material if one were to make a tablet. Thus, Makino does not remedy the deficiencies of Barry; and pending claim 17 and its dependent claims are inventive and non-obvious in view of those references.

Likewise, the combination of Barry and Makino fails to teach or suggest a method of preparing the product, and so claim 16 is also new and inventive.

*Frost & Makino*

It is also asserted that pending claims 3-6 and 8-17 would have been obvious to one of ordinary skill in the art in view of Frost over Makino. Applicants traverse the rejection. Both Frost and Makino are directed to fundamentally distinct objectives, neither of which is applicable here.

Frost is directed to a dosage form for the administration of 2', 3'-didesoxyadenosine (DDA) for the treatment of AIDS. The formulation includes DDA protected by one or more pharmaceutically inert layers, at least the outer one of which is stable in acidic pH and which dissolves in basic pH. This prevents the DDA from being exposed to gastrointestinal fluids until reaching the small intestine (p. 2, lines 1-8).

There are various embodiments. In one, there is a plurality of dosage subunits having three components: the active agent, DDA; pharmaceutically inert-

acid resistant layers; and an inert layer, e.g., nonpareil seeds. Those subunits are described as suitable for inclusion in a capsule; or in a matrix for formation into a compressed tablet (p. 2, lines 9-15). The matrix disintegrates in the GI tract to release the plurality of dosage subunits. This compressed tablet formulation requires the matrix material, which is obviated by the instant claims.

Elsewhere in Frost, the tablets are described as including a matrix of a polymer such as hydroxypropylmethylcellulose. The hydroxypropylmethyl-cellulose constitutes from about 5 to about 40% of the formulation (p.3, line 23-p. 4, line 12). Frost does not teach a tablet consisting essentially of neutral microgranules coated with an active principle mixture, and only 1% of a compression excipient. On the contrary, Frost clearly teaches those skilled in the art that very substantial quantities of a matrix or binder material is necessary to formulate tablets of this active agent.

For substantially the same reasons presented above in relation to Barry, Makino does not remedy the deficiencies of Frost. Makino does not teach a tablet consisting essentially of neutral microgranules coated with an active principle mixture; nor does it teach or suggest that a tablet can be made as described by Frost but without the matrix or binder material. Quite the contrary, Makino teaches the fabrication of coated granules that can be used in capsules or on their own. Makino has not been shown to teach or suggest that those granules can be compounded as tablets, with or without a matrix material. The absence of any teaching or suggestion that formulations such as those described by Frost can be compounded as tablets without any substantial matrix material is fatal to a *prima facie* of obviousness. Applicants respectfully submit that the rejection fails to make a *prima facie*

case of obviousness, and that pending claim 17 and its dependent claims are inventive over the cited references.

Likewise, and for at least the same reasons, the rejection fails to make a *prima facie* case of obviousness with respect to the process of claim 16 and the tableting premix of claim 11, and any respective dependent claims. Applicants request reconsideration and withdrawal of the rejection.

## CONCLUSION

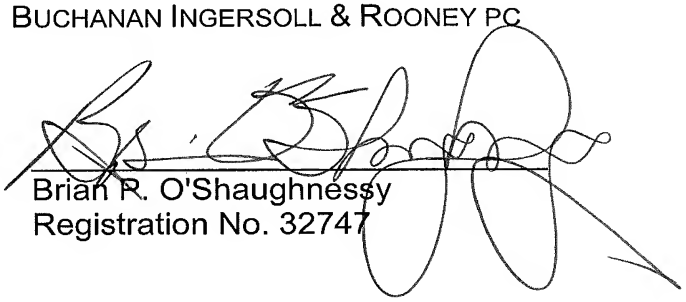
In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: August 28, 2009

By: 

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